08-23-04

In the United States Patent and Trademark Office

In re reissue patent application of:	Art Unit: 1616
Plachetka, et al.	Examiner: Choi, Frank I
Application No: 10/811,793	Current status of application:
(For reissue of Patent No.: 6,479,551)	Docketed New Case
Filing of Application: March 29, 2004	
For: Treatment of Migraine Headache	**ATTENTION: Bruce Kisliuk**

Protest Under 37 CFR 1.291(a)

Assistant Commissioner for Patents
Washington, DC 20231

To whom it may concern:

This protest is being filed on a reissue application within the 2-month period following the announcement of the reissue application in the *Official Gazette* on June 22, 2004.

Pursuant to 37 CFR 1.291(b):

1) A listing of patent, publications, and other information relied upon can be found in the enclosed PTO-1449 form.

2) A concise explanation of the relevance of each listed item is included herewith.

3) A copy of each listed patent, publication, or other item of information in written form, or pertinent portions thereof is enclosed.

Please send acknowledgement of receipt of this paper via the self-addressed, stamped postcard included.

Summary of documents

Patent Documents

U.S. Patent 4,380,540, Poyser et al., 4/1983.*

Poyser teaches analgesic tablets containing metoclopramide in combination with paracetamol, a non-acidic analgesic.

U.S. Patent 5,288,507, Sims et al., 2/1994.

Sims teaches a composition including iburprofen, metoclopramide and an antacid for the treatment of pain.

U.S. Patent 5,415,870, Gergely et al., 5/1995

Gergely teaches a method of combining an acid and a base in storage stabilized dosage form.

U.S. Patent 6,106,862, Chen et al., 8/2000

Chen teaches the formulation of long-acting, controlled release analgesic tablets.

European Patent EP0823255 A1, Seiyaku et al., 11/1998

Seiyaku teaches the combination of sucralfate and an analgesic in a multilayer tablet.

Non-patent literature

Greiff, "Pharmacokinetic drug interactions with gastrointestinal motility modifying agents," *Clin Pharmacokinetics* (1994) 27(6): 447-461.*

Greiff describes the effects of metoclopramide on the absorption of other drugs,

Moore, "Drug treatment of migraine: Part I. Acute therapy and drug-rebound headache," *Am Fam Physician* (1997) 56(8): 2039-48.

Moore teaches the administration of an NSAID 20-30 minutes after administration of metoclopramide for the treatment of migraines.

Saadah, "Abortive migraine therapy with oral naproxen sodium plus metoclopramide plus ergotamine tartrate with caffeine," *Headache* (1992) 32:95-97.*

Saadah teaches a combination of metoclopramide and naproxen for the treatment of migraine.

* References already cited in the reissue application are not enclosed herewith.

Arguments

35 U.S.C. 112 Arguments

Claims 6, 7, and 9 should be rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention. It is unclear from Claims 6, 7 and 9 how it is possible to coordinate ("sequentially administer") two drugs which are in unit dosage form ("one administration entity containing two drugs"), as defined in the patent for which this application is a reissue (col. 8, lines 50-51; col. 10, lines 17-18). Perhaps the inventor intended to disclose a "sequentially dissoluble tablet."

35 U.S.C. 103 Arguments

Claim 5 should be rejected under 35 U.S.C. 103(a) as being unpatentable over Saadah in view of Gergely. Saadah teaches the use of a combination of metoclopramide and naproxen sodium for the treatment of a migraine headache but does not teach the two compounds in unit dosage form (page 95). Gergely teaches a method of combining an acid (e.g. naproxen) and a base (e.g. metoclopramide) in storage stabilized dosage form with a potency reduction of not more than 15% (col. 4, line 62). It would have been obvious to a person having ordinary skill in the art to provide the metoclopramide and naproxen sodium of Saadah in an acid-base storage stabilized dosage form, as disclosed by Gergely, to have metoclopramide and naproxen in a stabilized unit dosage form for ease of use. In reference to claims 6-13, 22-29 and 34-41, Gergely and Saadah teach the combination an analgesic and metoclopramide in unit dosage form.

Alternatively, Claim 5 should be rejected under 35 U.S.C. 103(a) as being unpatentable over Sims in view of Saadah, in further view of Gergely. Sims teaches a composition including ibuprofen, metoclopramide, and an antacid for the treatment of pain, wherein the composition has a faster onset of action than the analgesic alone (col. 1, lines 45-57; col. 4, lines 61-68). Sims does not teach a composition which includes naproxen. Saadah teaches a combination of metoclopramide and naproxen sodium for the treatment of migraine (page 95). It would have been obvious to one having ordinary skill in the art to replace ibuprofen with another NSAID such as naproxen for the treatment of migraine. It is not clear whether the presence of an antacid in the Sims composition is sufficient to create acid-base storage stabilization. However, Gergely teaches a method for acid-base storage stabilization (col. 2, lines 33-38; col. 4, lines 57-64). Therefore, it would have been obvious to a person having ordinary skill in the art to create an acid-base stabilized storage composition of metoclopramide, antacid, and naproxen for an effective migraine treatment having a longer shelf life.

Claims 6 and 14-18 should be rejected under 35 U.S.C. 103(a) as being unpatentable over Moore in view of Greiff, in further view of Gergely and Saadah. According to the specification of the patent for which this application is a reissue, a "coordinated" dose means a dose in which metoclopramide and another drug are sequentially administered, and wherein metoclopramide has an effective concentration between 1 and 30 minutes after administration, and the other drug, in this case, an analgesic, is available at a therapeutically effective level in 5 to 60 minutes after

administration (col. 8, lines 50-58). The specification further requires that the analgesic effect should not be attained until after metoclopramide is present at an effective local gastrointestinal concentration (col. 8, lines 58-61).

According to Greiff and Moore, the coordination of metoclopramide and an NSAID will result in an effective amount of NSAID with 42.5-52.5 minutes following administration of metoclopramide. Greiff generally describes the effects of metoclopramide on the absorption of other drugs. Greiff states, "It should be expected that the rate of absorption of orally administered drugs will be increased when they are given with prokinetic drugs. In general, this is confirmed by much of the data presented in this review" (page 448, col. 1). Greiff further discusses the interaction of metoclopramide with a broad range of other drugs (pages 448-455), but does not disclose the timing of administration of an NSAID following administration of metoclopramide.

Moore teaches that an NSAID should be administered 20-30 minutes after administration of metoclopramide (4th page of printout). Moore does not specifically teach how much time elapses between administration of metoclopramide and the presence of an effective concentration of metoclopramide in the blood plasma. However, it is an inherent property of metoclopramide that it reaches an effective dose within 20 minutes (see specification of patent for which this application is a reissue, col. 8, lines 40-43). It is not an inherent property of metoclopramide, nor is it evident from Moore, how long it takes for an NSAID to reach an effective concentration following

administration of the NSAID with metoclopramide. Greiff teaches that the administration of an NSAID with metoclopramide will be effective 22.5 minutes after administration of the NSAID (page 449). Therefore, according to Moore and Greiff, the NSAID is effective about 42.5-52.5 minutes after administration, which is within the 5-60 minutes period prescribed by the specification. As a result, it would have been obvious to an ordinarily skilled artisan how to "coordinate" metoclopramide and an analgesic to be effective in reducing or eliminating pain associated with migraine headaches. In reference to Claim 15, Greiff describes the effect of the co-administration of acetylsalicylic acid with metoclopramide in patients having gastric stasis (p. 449). In reference to Claim 16, Greiff describes the co-administration of acetylsalicylic acid for treatment of a migraine attack (p 449). In reference to Claims 17-18, Greiff describes the use of acetylsalicylic acid, which is both an analgesic and an NSAID (page 449, col. 2 through page 450, col. 1). In reference to Claims 20-21, Saadah describes the use of naproxen as claimed (page 95).

In further reference to Claim 7, 10 and 13, Greiff, Moore, Saadah and Gergely teach the combination of an NSAID and metoclopramide in the form of a tablet (Greiff, page 449; Moore, page 4 of printout; Saadah, page 95; and Gergely, col. 2, lines 33-38 and col. 4, lines 57-64). In further reference to Claim 9, a 5HT agonist vasoactive agent is not part of any of the references. Further in reference to Claims 11 and 12, naproxen provided in Saadah is one of the drugs in the group claimed (page 95).

Claim 8 should be rejected as unpatentable under 35 U.S.C. 103(a) as obvious over Moore and Greiff, in view of Saadah and Gergely, in further view of Seiyaku. Moore, Greiff, Saadah and Gergely teach the combination of an analgesic and metoclopramide in the form of a tablet, but do not teach that the tablet should be in the form of a multilayer tablet. Seiyaku teaches the combination of sucralfate and an analgesic in a multilayer tablet (page 3, line 40). It would have been obvious to a person having ordinary skill in the art to replace the sucralfate of Seiyaku with metoclopramide for the purpose of protecting a patient's digestive system from irritation due to the analgesic.

Claims 13, 19, 25, and 41 should be rejected under 35 U.S.C. 103(a) as obvious over Chen, in view of the discussion of Claims 10, 14, 22 and 34-35, respectively. The references variously teach combinations of metoclopramide and an analgesic, but do not teach the formulation of a long-acting analgesic. Chen teaches the formulation of long-acting analgesics, including NSAIDS further including naproxen (col. 3, lines 11-16). It would have been obvious to a person having ordinary skill in the art to apply Chen to Claims 10, 14, 22 and 34-35 to create a simpler dosing schedule and encourage patient compliance.

Claim 22 should be rejected under 35 U.S.C. 103(a) as obvious over Greiff and Moore, in view of Poyser. Greiff and Moore teach the claimed method as described in the analysis regarding claims 6 and 14. Greiff and Moore do not teach a non-acidic analgesic. Poyser teaches the use of metoclopramide in combination with paracetamol which is a non-acidic analgesic (col. 1, lines 19-27). It would have been obvious to a person having ordinary skill in the art to use a non-acidic analgesic as taught by Poyser

in place of acetylsalicylic acid as described in Greiff and Moore to prevent an interaction between the analgesic and metoclopramide. In reference to Claim 23, Poyser teaches a combination in the form of a tablet. In reference to Claim 24, Poyser teaches a combination which does not include a 5HT agonist vasoactive agent. In reference to Claim 25, Chen teaches the formulation of a long-acting NSAID (col. 3, lines 11-16). In reference to Claim 29, Chen teaches the formulation of an analgesic that is long-acting (col. 1, lines 3-6).

Claim 34 should be rejected under 35 U.S.C. 103(a) as obvious over Saadah and Gergely, in view of Seiyaku. Saadah (page 95) and Gergely (col. 2, lines 33-38; col. 4, lines 57-64) teach an acid-base storage stabilized tablet, but do not teach a multilayer tablet. Seiyaku teaches a multilayer tablet (pages 4-5, Examples 2 and 3). It would have been obvious to one having ordinary skill in the art to make the tablet of Saadah and Gergely as a multilayered tablet to facilitate tablet dissolution.

Claim 35 should be rejected under 35 U.S.C. 103(a) as obvious over Gergely and Saadah, in view of Greiff and Moore. Gergely and Saadah teach a unit dosage form of metoclopramide and an analgesic which is acid-base storage stabilized. Greiff (page 449) and Moore (page 4 of printout) teach the coordination of metoclopramide and an analgesic. It would have been obvious to combine the acid-base storage stabilized tablet from Gergely (col. 2, lines 33-38 and col. 4, lines 57-64) and Saadah (page 95) with the coordinated dosing of Greiff and Moore to create a tablet that is easy to administer and store, and which effectively treats migraine headaches. In reference to claim 36, Gergely describes a tablet which has separate coating for an acid and a base component of a multilayer tablet (col. 11, lines 34-38). In further reference to claim 37,

the tablet described does not contain a 5HT agonist vasoactive agent. In further reference to claim 38-40, Saadah (page 95) teaches naproxen as the analgesic.

Conclusion

Protestor respectfully requests that claims 5-25, 29, 34-41 be rejected.

Respectfully submitted on this 20th day of August, 2004,

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CERTIFICATE OF SERVICE

A copy of this paper has been served upon the attorney of record, Michael A. Sanzo by first-class mail on August 20, 2004.

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